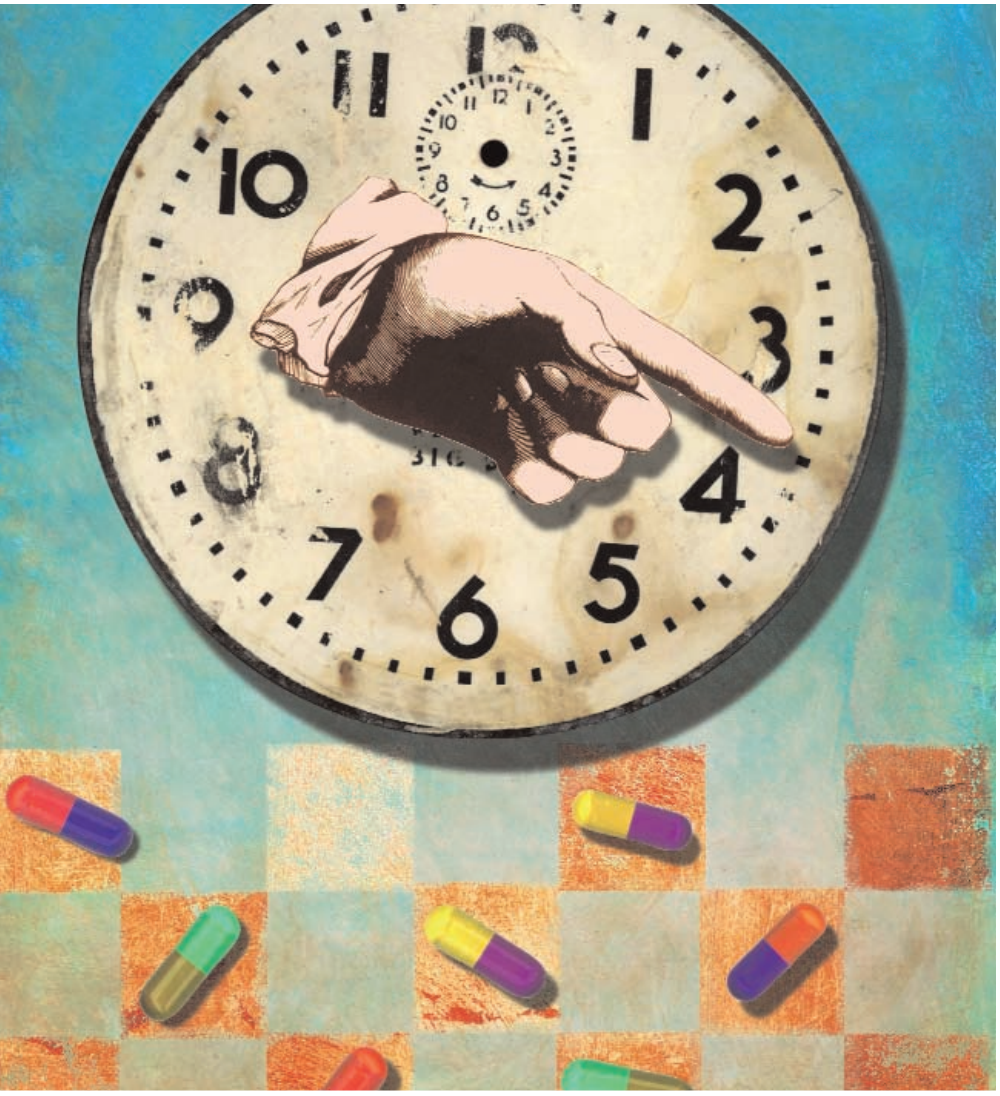
Research to Practice



WHEN COMMON CLINICAL PRACTICE MEETS EVIDENCE-BASED MEDICINE

by David Feifel, MD, PhD

When one lives in the academic world of medicine, one is aware of certain tensions between popular clinical practices and those that are evidence-based. Over the years, I've become aware that there are a number of common clinical practices that are out of step with the body of research findings. In this column, I hope to periodically to address some of these "disconnects" between clinical practice and research evidence.

There is a "disconnect" between common clinical practice and research findings when it comes to dosing selective serotonin reuptake inhibitors (SSRIs) for depression. Typically, psychiatrists and primary care physicians start depressed patients at the lower end of the therapeutic dose range of an SSRI. This would be the equivalent of 20mg/day of fluoxetine, for example. After providing what is felt by the physician to be an appropriate therapeutic trial at that dose, it is a very common practice to increase the dose of the SSRI if a patient does not get an adequate response. Sometimes several dose increases of the same SSRI are attempted in order to extract a therapeutic benefit before moving on to another medication. But, is there good evidence that increasing doses of SSRIs increase their antidepressant efficacy? Is this is a reasonable strategy for overcoming poor responses to lower doses?

There is a large, but still inadequate, body of research into this topic, and it takes a number of different forms. Let's start with some of the basic science research relevant to this question. SSRIs are recognized to work by binding to the serotonin transporters in the brain, which are responsible for reuptake of serotonin from the synaptic cleft. By binding and functionally blocking these transporters, SSRIs increase available serotonin in the synapse. Positron emission tomography (PET) binding studies in humans clearly show that at the lowest therapeutic doses of five SSRIs currently on the market, serotonin transporter occupancy is quite high. Furthermore, increasing doses beyond this minimal therapeutic threshold produces very little change in the percentage

of serotonin transporters occupied.[1] There does not, therefore, appear to be an obvious neurobiological rationale for increasing the dose of an SSRI nor a rationale that can explain the perception or anecdotal experiences of clinicians that such dose increases can be clinically beneficial in depression.

So what does the clinical research show about the practice of increasing the dose of an SSRI? One genre of studies that can inform us on this issue are "fixed-dose" trials with SSRIs. These are trials in which patients are randomly assigned to either a placebo or one of several different doses of a given SSRI from the outset. Most SSRIs have been investigated using at least one fixed-dose study as part of their clinical trials program for Food and Drug Administration (FDA) approval. The overwhelming finding from these studies is that the SSRIs are equally effective across the therapeutic dose ranges (e.g., 20–60mg/day of fluoxetine or the equivalent of another SSRI).[2] Thus, the fixed-dose trials comport nicely with the pharmacodynamic findings of Meyer, et al.,[1] and both cast doubt on the practice of increasing SSRI dose in depression.

But one could counter that these fixed-dose studies do not exactly address the issue of whether a patient who is not responding to a low dose of an SSRI could be reasonably expected to respond to a higher dose. Indeed, this is true because randomly assigning depressed subjects to one of several doses of a drug is not the same as starting all depressed patients on an SSRI and selectively increasing the dose only in those that do not benefit from the initial dose. Fortunately, another set of studies addresses this clinically relevant question more appropriately. For example, Schweizer, et al.,[3,4] used an elegant experimental design to address this question. In one published study, Schweizer, et al.,[3] started depressed research volunteers on a low therapeutic dose of a fluoxetine (20mg/day). After a three-week trial on this dose, those subjects who did not respond according to preestablished criteria were randomly assigned to continue with low-dose fluoxetine (20mg/day) or to a higher dose of this SSRI (60mg/day). The result revealed that the proportion of originally unresponsive patients who subsequently converted to responders did not differ between those in the continued low-dose and high-dose treatment conditions. Schweizer, et al.,[4] later replicated this finding using sertraline. These studies suggest that it is not the change in dose that produces the improvements in originally unresponsive treatments that many clinicians experience, but rather the additional time on the SSRI.

We can now understand how clinicians working with one depressed patient at a time might develop a "superstitious" belief that increasing the SSRI dose produces stronger antidepressant effects. A common scenario might play out as follows:

After 3 or 4 weeks on the starting dose of an SSRI the patient reports no benefit so the clinician doubles the dose. After another 3 or 4 weeks the patient still has not felt any improvement and the clinician raises the dose yet again. At the next appointment, the patient looks brighter and reports that, shortly after the last dose increase, he began to experience a distinct improvement in his depression symptoms. The clinician is delighted, and this reinforces her strategy of increasing SSRI doses when patients do not respond to starting doses. The patient indicates that there is a significant downside: He has developed side effects that also emerged since the last dose change. The clinician sympathizes, but informs the patient that this is just the price he will have to pay since he's been unresponsive to lower doses.

Anecdotal experiences like this can produce powerful beliefs in

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clinicians about causal relations between their actions and patients' responses. Unfortunately, treating one patient at a time with no control for the increasing dose, as is the nature of clinical practice, precludes the ability of the clinician to differentiate the effects of time from those of dose. That's why research studies with clinically relevant designs, like the ones performed by Schweizer's group, are so important—and more are needed.

It is important to realize that research findings like the ones described here are too few, and even the ones available can only inform us about general principles. They can never tell us about whether it will or will not work in an individual patient. Therefore, I cannot argue that some patients do not respond differentially across the therapeutic dose range of SSRIs. However, it seems that the many weeks required to execute a stepwise dose increase strategy is a poor way to practice when the evidence indicates that the average patient will not be affected simply by the dose change.

Dr. Feifel welcomes comments at dfeifel@ucsd.edu.

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